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1 575 310

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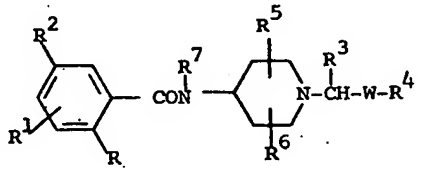
(54) PIPERIDINE DERIVATIVES

(71) We, ANPHAN S.A., a Spanish Body Corporate, of Cerida Street No. 9, Madrid, Spain, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new therapeutically useful piperidine derivatives, to processes for their preparation and pharmaceutical compositions containing them.

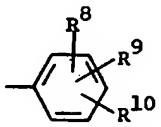
The new piperidine derivatives of the present invention are those compounds of the general formula:



I

[where R represents a halogen atom or a hydroxy or lower alkynyloxy (e.g. propargyloxy) group, or a lower acyloxy group in which the acyl moiety is derived from a carboxylic acid (preferably a lower alkanoyloxy, e.g. acetoxy, group), or an aralkyloxy (preferably a phenyl(lower) alkyloxy, e.g. benzyloxy) group, R^1 and R^2, which may be the same or different, each represent a hydrogen or halogen atom, or a sulphamoyl (i.e. $-SO_2NH_2$), amino, lower alkylamino, di(lower)alkylamino, lower alkylsulphonyl or N-lower alkylsulphamoyl group, or a lower acylamino group in which the acyl moiety is derived from a carboxylic acid, including trifluoroacetic acid (preferably a lower alkanoylamino group), the group represented by the symbol R^1 (when other than a hydrogen atom) being in the 3- or 4-position of the phenyl ring, with the proviso that R^1 and R^2 do not both represent hydrogen atoms; R^3 represents a hydrogen atom or a lower alkyl or lower alkenyl group, or a cycloalkyl or cycloalkenyl group having from 3 to 7 carbon atoms in the ring; or a phenyl group, R^4 represents a cycloalkyl or cycloalkenyl group having from 3 to 7 carbon atoms in the ring, an aroyl, (e.g. benzoyl), aryl (e.g. phenyl or naphthyl) or heterocyclyl (e.g. thienyl, pyridyl or pyrimidinyl) group; R^5, R^6 and R^7 each represent a hydrogen atom, a lower alkyl, lower alkenyl (e.g. $-CH_2-CH=CH_2$) or a benzyl group, and W represents a single bond or a lower alkylene (e.g. $-CH_2-$ or $-CH_2CH_2-$) or lower alkenylene (e.g., $-CH=CH-$ or $-CH_2-CH=CH-$) group] and pharmacologically-acceptable salts, quaternary ammonium salts or N-oxide derivatives thereof.

The aryl group represented by R^4 may be a phenyl group of the general formula:

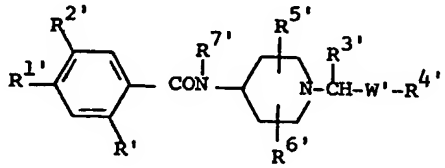


II

wherein R^8, R^9 and R^{10} each represent a hydrogen or halogen atom, or a lower alkoxy, hydroxy, nitro, amino, lower alkylamino, lower dialkylamino, trifluoromethyl or lower alkyl group, or R^8 and R^9 together may form a methylenedioxy group in which case R^{10} represents a hydrogen atom.

The qualification "lower" as applied herein to alkyl, alkenyl, alkylene, alkenylene, alkoxy, alkynyloxy, acyl, acyloxy, alkanoyloxy and alkanoyl groups means that the group in question contains at most 6 carbon atoms.

Preferred compounds of general formula I are those of the more specific formula:



III

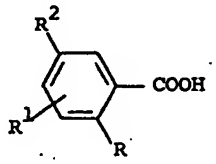
[where R' represents a halogen (preferably chlorine) atom or a hydroxy or lower alkynyloxy (preferably propargyloxy) group, or a lower acyloxy group in which the acyl moiety is derived from a carboxylic acid (preferably acetoxy), or a phenyl(lower)alkyloxy (preferably benzyloxy) group; R1' represents a hydrogen atom or an amino or lower alkylamino (preferably methylamino) group, or a lower acylamino group in which the acyl moiety is derived from a carboxylic acid (preferably a lower alkanoylamino group, e.g. acetamido or trifluoroacetamido), R2' represents a hydrogen or halogen (preferably chlorine or bromine) atom or a lower alkylsulphonyl (preferably methylsulphonyl) group, with the proviso that R1' and R2' do not both represent hydrogen atoms; R3' represents a hydrogen atom, a lower alkyl (preferably methyl) or a phenyl group; R4' represents a cyclohexyl, cyclohexenyl (e.g. cyclohex-3-enyl) or cyclohexadienyl group optionally substituted by a lower alkyl (preferably methyl) group, or R4' represents a phenyl group optionally substituted by one or two halogen atoms or lower alkyl or lower alkoxy groups, or by a methylenedioxy or trifluoromethyl group, or by three methoxy groups, or R4' represents a thienyl group or a benzoyl group optionally substituted by a halogen atom (preferably *p*-fluorobenzoyl); R5' represents a hydrogen atom or a lower alkyl (preferably methyl) group; R6' and R7' each represent a hydrogen atom or a lower alkyl preferably methyl or ethyl) group, and W' represents a single bond or a methylene, ethylene or vinylene group] and pharmaceutically acceptable acid addition salts thereof.

Of outstanding importance are those compounds of general formula III wherein R' represents a propargyloxy group, R1' represents a methylamino or, preferably, an amino group, R2' represents a bromine or, preferably, chlorine atom, R3' and R7' each represent a hydrogen atom, R4' represents a cyclohexyl group, a cyclohexa-1,4-dienyl group optionally substituted by a methyl group, or a phenyl group optionally substituted by a halogen atom or a methyl or methoxy group (preferably in the *para*-position), R5' and R6' are the same or different and each represents a methyl group or, preferably, a hydrogen atom, and W' represents a methylene group or, preferably, a single bond.

Especially preferred compounds of the present invention are N - (1 - *p* - fluorobenzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, N - [1 - (4 - methylcyclohexa - 1,4 - dienyl)methylpiperid - 4 - yl] - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, N - (1 - *p* - methylbenzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, N - (1 - *p* - chlorobenzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, N - (1 - cyclohexa - 1',4' - dienylmethylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide and N - (1 - benzylpiperid - 4 - yl) - 2 - propargyloxy - 4 -

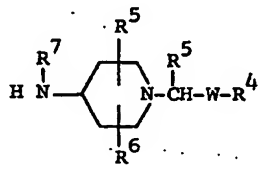
amino - 5 - chlorobenzamide, and their pharmacologically-acceptable acid addition salts.

According to a feature of the present invention, the compounds of general formula I are prepared by the process which comprises reacting a reactive derivative of a benzoic acid of the general formula:



IV

(wherein R, R^1 and R^2 are as hereinbefore defined) with a piperidine derivative of the general formula:



V

wherein the various symbols are as hereinbefore defined. The reactive derivative of the said benzoic acid may be a halide (preferably chloride), an alkyl ester (preferably methyl ester), an anhydride or a mixed anhydride.

The reaction is preferably carried out in the presence of an inert organic solvent, for example benzene, toluene, chloroform, tetrahydrofuran, N,N-dimethylformamide or dioxan, at a temperature between −5° and 120°C.

Halides of the benzoic acids of general formula IV can be prepared by reaction of the acid with thionyl chloride or a phosphorus halide in the presence of an inert organic solvent such as benzene, toluene or a halogenated hydrocarbon. Mixed anhydrides of the benzoic acids of general formula IV can be prepared by the reaction of the acid with, for example, an alkyl chloroformate in the presence of an organic nitrogen-containing base, e.g. triethylamine, in an inert organic solvent, e.g. tetrahydrofuran, methylene chloride or N,N-dimethylformamide, and at a temperature between −20° and +25°C. Esters and anhydrides of the benzoic acids of formula IV, which may be employed as starting materials in the aforementioned process, can be prepared from the benzoic acids by methods known *per se*.

The piperidine derivatives of general formula V wherein R^7 is a hydrogen atom can be prepared by reduction of corresponding 4-piperidone oximes with lithium aluminium hydride in the presence of diethyl ether or tetrahydrofuran, or by reductive amination of corresponding 4-piperidones dissolved in an organic solvent, e.g. an alcohol containing from 1 to 4 carbon atoms, in the presence of platinum or Raney nickel as catalyst. The piperidine derivatives of general formula V wherein R^3 or/and R^4 is or are a cyclohexadienyl group can be prepared from the corresponding compounds of general formula V wherein R^3 or/and R^4 is or are a phenyl group by reduction with lithium in liquid ammonium or a lower alkylamine. The piperidine derivatives of general formula V wherein R^7 is a lower alkyl, a lower alkenyl or a benzyl group can be prepared from the corresponding N-acyl substituted compounds by reduction of the carbonyl group therein to methylene using lithium aluminium hydride.

Other piperidine derivatives of general formula V can be prepared by methods known *per se*.

The piperidine derivatives of general formula I are also prepared, according to a further feature of the invention, by the direct reaction of a benzoic acid of general formula IV with a piperidine derivative of general formula V in the presence of an appropriate dehydrating agent. Such agents are silicon tetrachloride, a mono-, di- or trialkyl-silyl chloride, titanium tetrachloride, N,N'-dicyclohexylcarbodiimide, thionyl chloride, sulphur trioxide in dimethyl sulphoxide, toluene-*p*-sulphonyl chloride, acetone dimethyl acetal or a polymeric dehydrating agent. The reaction is carried out in an inert organic solvent, e.g. methylene chloride, acetone, pyridine, ethyl acetate or dioxan, at a temperature between 20° and 110°C.

The piperidine derivatives of general formula I wherein R represents a

hydroxy group are prepared, according to a further feature of the invention, from the corresponding O-methylated derivatives of general formula I (viz. R represents a methoxy group) by the process which comprises reaction of such compounds with boron tribromide or aluminium trichloride using methylene chloride or benzene as solvent medium at a temperature between 20° and 80°C.

The O-methylated compounds employed as starting materials in this process may be prepared by similar processes as hereinbefore described for the preparation of piperidine derivatives of general formula I but using instead a benzoic acid of general formula IV or reactive derivative thereof wherein R represents the methoxy group (see, for example, the procedures described in the Complete Specification of our British Patent Application No. 12572/74 and 35402/74, Serial No. 1,507,462).

The piperidine derivatives of general formula I wherein R represents a hydroxy group are prepared, according to another feature of the invention, from the corresponding O-benzylated or O-acylated derivatives of general formula I, viz. R represents a benzyloxy or acyloxy group respectively. When an O-benzylated derivative is used, the process comprises a debenzylation with hydrogen preferably in the presence of palladium as catalyst using an alcohol containing from 1 to 4 carbon atoms as solvent medium and at a temperature between 15° and 45°C. When an O-acylated derivative is used as starting material, the piperidine derivatives of general formula I wherein R represents a hydroxy group are prepared by acid or alkaline hydrolysis, preferably with hydrochloric acid or sodium hydroxide respectively using a mixture of water and an alcohol containing from 1 to 4 carbon atoms as solvent medium, at a temperature between 20° and 90°C.

In the preparation of those compounds of general formula I wherein the symbol(s) R^1 and/or R^2 represent(s) an amino group by the aforementioned processes, it is sometimes advisable to use as starting material corresponding compounds in which the amino group is protected by an acyl group, the acyl protecting group preferably being acetyl, chloroacetyl, trifluoroacetyl or phthaloyl. After the reaction the N-acylated intermediate products are subjected to acid or alkaline hydrolysis to give the corresponding compounds of general formula I in which R^1 and/or R^2 represent(s) an amino group. Acid hydrolysis of the N-acylated intermediate compounds may be carried out by heating with dilute hydrochloric acid, preferably at the boiling point of the reaction mixture, while alkaline hydrolysis is preferably carried out at room temperature with sodium or potassium hydroxide in an aqueous-alcoholic solution.

The piperidine derivatives of general formula I have as their principal pharmacological properties the ability to antagonise the effects of dopamine or dopaminergic agents of endogenous or exogenous origin and to cause stimulation of serotoninergic mechanisms. In those circumstances where homeostatic control is a balance between dopaminergic and serotoninergic mechanisms these two actions are synergistic and the precise contribution of each one to the final biological response is difficult to determine. As a group they have exhibited activities which may be considered beneficial in the treatment of obesity and a variety of gastrointestinal and cerebral malfunctions in mammals, including man. Their characteristic properties in experimental animals are antagonsim of the effects of dopaminergic agents such as apomorphine, induction of catatonia, production of local anaesthesia, stimulation of gastrointestinal transit and induction of both spasmogenic and spasmolytic effects on smooth muscle according to the initial resting tone.

Nevertheless, as within the series antidopaminergic, serontoninergic and local anaesthetic potency do not necessarily run in parallel, the clincal applications of the various derivatives may well be different. As a group they may be useful as anorectic drugs in the treatment of obesity, and be effective in the treatment of nausea and vomiting of diverse origin such as that resulting from gastrointestinal disorders, congestive heart failure and post-operative conditions, as well as in the treatment of other gastrointestinal disorders such as dyspepsia, flatulance, bile regurgitation, hiatus herna, peptic ulcer, reflux oesophagitis, gastritis, duodenitis and cholelithiasis. They may also be useful in the treatment of a variety of conditions affecting the central nervous system such as acute and chronic psychosis, manic psychosis, schizophrenias, serious disturbances of behaviour and non-melancholic depressive states and migraine.

For therapeutic purposes the compounds of general formula I may be employed in the form of biologically and pharmacologically-acceptable inorganic or

organic acid addition salts such as sulphates, hydrohalides (e.g. hydrochlorides), phosphates, lower alkanesulphonates, arylsulphonates, and salts of aliphatic or aromatic acids containing from 1 to 20 carbon atoms which may contain one or more double bonds, or other functional groups such as hydroxy, lower alkoxy, amino or keto, e.g. fumarates.

The piperidine derivatives of general formula I wherein R represents a hydroxy group may also form pharmacologically-acceptable salts with alkali or alkaline earth metals, which salts are formed by reaction of the derivatives of formula I wherein R is a hydroxy group with an alkali metal or alkaline earth metal carbonate or hydroxide using water, methanol or ethanol, as solvent at a temperature between 40° and 100°C.

They may also be used for therapeutic purposes in the form of pharmacologically-acceptable quaternary ammonium salts such as those salts formed by reaction of the compounds of general formula I with lower alkyl halides or sulphates, or in the form of oxygenated derivatives in which oxygen is attached to the nitrogen atom of the piperidine nucleus, viz. the N-oxides.

The pharmacologically-acceptable acid addition salts, quaternary ammonium salts and N-oxides of the piperidine derivatives of general formula I may be prepared by methods known *per se*.

Also included within the scope of the present invention are pharmaceutical compositions which comprise, as active ingredient, at least one compound of general formula I or a pharmacologically-acceptable acid addition salt, alkali metal or alkaline earth metal salt, or quaternary ammonium salt thereof or N-oxide thereof, in association with a pharmaceutically-accetable carrier or diluent. Preferably the compositions are made up in a form suitable for oral, topical, percutaneous or parenteral administration.

The pharmaceutically-acceptable carriers or diluents which are admixed with the active compound, or compounds, or salts or N-oxides of such compounds, to form the compositions of this invention are well known *per se* and the actual excipients used depend *inter alia* on the intended method of administering the compositions. Compositions of this invention are preferably adapted for administration *per os*. In this case, the compositions for oral administration may take the form of tablets, capsules, lozenges or effervescent granules or liquid preparations, such as mixtures, elixirs, syrups or suspensions, all containing one or more compounds of the invention; such preparations may be made by methods well known in the art.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredients, together with colouring or flavouring agents, if desired. Tablets or capsules may conveniently contain between 0.5 and 100 mg, and preferably from 0.5 to 25 mg, of active ingredient or the equivalent amount of an acid addition, alkali or alkaline earth metal or quaternary ammonium salt thereof, or N-oxide thereof.

The liquid compositions adapted for oral use may be in the form of solutions or suspensions. The solutions may be aqueous solutions of a soluble salt or other derivative of the active compound in association with, for example, sucrose to form a syrup. The suspensions may comprise an insoluble active compound of the invention or an acid addition, alkali or alkaline earth metal, or quaternary ammonium salt thereof in association with water, together with a suspending agent or flavouring agent.

Compositions for parenteral injection may be prepared from soluble salts, which may or may not be freeze-dried and which may be dissolved in water or an appropriate parenteral injection fluid.

In other aspect of the invention, the compounds may be mixed with other active anti-acid and anti-ulcer agents (excluding anticholinergic agents) for oral or, in appropriate cases, for parenteral use.

The following Examples illustrate the preparation of piperidine compounds of the present invention.

EXAMPLE 1

A solution of N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - chlorobenzamide (18.7 g; 0.05 moles) in methylene chloride (300 ml) was added to another solution of boron tribromide (14.2 ml; 0.15 moles) in methylene chloride (75 ml). The mixture was stirred at room temperature for 24 hours and then poured into a mixture of a saturated solution of sodium bicarbonate in water (2 litres) and methylene chloride (1 litre). The organic solution was dried and the solvent

removed *in vacuo* to give a paste which was triturated with petroleum ether. The residue obtained was treated with a saturated solution of ethanolic hydrogen chloride to give N - (1 - benzylpiperid - 4 - yl) - 2 - hydroxy - 4 - amino - 5 - chlorobenzamide hydrochloride (12 g), m.p. 173°—175°C.

N - (1 - Benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - chlorobenzamide employed as starting material was prepared as follows:—

A solution of 2 - methoxy - 4 - amino - 5 - chlorobenzoic acid (15.1 g; 0.075 moles) in 150 ml of dry tetrahydrofuran was cooled to −15 to −10°C. Triethylamine (10.5 ml; 0.075 moles) in 30 ml of dry tetrahydrofuran was slowly added, followed by ethyl chloroformate (7.05 ml; 0.075 moles) also dissolved in dry tetrahydrofuran.

Stirring was maintained for 1 hour at −15 to −10°C and then 1 - benzyl - 4 - aminopiperidine (14.26 g; 0.075 moles) in 30 ml of tetrahydrofuran were added. The temperature of the reaction mixture was allowed to reach ambient temperature with agitation and was maintained at this temperature for 6 hours, at the end of which the precipitate was filtered off. The organic extracts were concentrated at low temperature, the residue was dissolved in chloroform and the solution was washed several times with water.

The chloroform extracts were concentrated at low temperature to yield a paste which was dissolved in warm diethyl ether and allowed to crystallize. 21.2 g of a white solid, N - (1 - benzylpiperid - 4 - yl) - 2 - methoxy - 4 - amino - 5 - chlorobenzamide, m.p. 193—195°C, were obtained.

2 - Methoxy - 4 - amino - 5 - chlorobenzoic acid was prepared in the following manner:—

p-Aminosalicylic acid (30.6 g; 0.2 moles) and 100 cc of ethanol were introduced into a 250 ml flask, and the mixture was heated to 40°C. Acetic anhydride (20.4 g; 0.2 moles) was then added at such a rate that the temperature did not exceed 50°C. When the addition was complete, the mixture was stirred at 50°C for 3 hours. The product, 4-acetamidosalicylic acid (36 g), was filtered off; m.p. 235°C.

4 - Acetamidosalicylic acid (34 g; 0.17 moles), potassium carbonate (57.96 g; 0.42 moles) and 250 ml of acetone were introduced into a 500 cc flask and the mixture was heated to 40°C. Then, maintaining the same temperature, methyl sulphate (51.40 g; 0.408 moles) was added over approximately 15 minutes, and the mixture was then heated under reflux for 5 hours. The mixture was cooled, the potassium sulphate precipitate was filtered off and the acetone solution was concentrated to 1/3 of its original volume. Dilution with diethyl ether gave a crystalline solid which was filtered off. Methyl 2 - methoxy - 4 - acetamidobenzoate (34 g), m.p. 130—132°C, was thus obtained.

Methyl 2 - methoxy - 4 - acetamidobenzoate (34.8 g), 180 ml of acetic acid and a trace of ferric chloride were introduced into a 500 cc flask, provided with an agitator, a thermometer and a gas inlet. The solids were dissolved by heating and the solution was cooled to 15°C. Maintaining this temperature, a current of chlorine was passed through the solution, the reaction being controlled by cooling, until the weight had increased by 11.2 g. The solution obtained was poured into 2 litres of water, precipitating a white solid, which was filtered off to yield methyl 2 - methoxy - 4 - acetamido - 5 - chlorobenzoate (33 g), m.p. 149—152°C.

Methyl 2- - methoxy - 4 - acetamido - 5 - chlorobenzoate (25.75 g; 0.1 moles), suspended in 100 ml of ethanol, was introduced into a 500 ml flask. 40 g of sodium hydroxide, dissolved in 150 cc of water, were added and the mixture was heated under reflux for 2.5 hours. The mixture was diluted with water and made acid with concentrated hydrochloric acid. The white solid which precipitated was collected and recrystallised from methanol to give 2 - methoxy - 4 - amino - 5 - chlorobenzoic acid (17 g), m.p. 213—215°C.

EXAMPLE 2

A suspension of N - (1 - benzylpiperid - 4 - yl) - 2 - hydroxy - 4 - amino - 5 - chlorobenzamide (5 g; 0.014 moles) [prepared as described in Example 1] in 2N aqueous sodium hydroxide solution (250 ml) was heated until dissolution was complete. On cooling, the sodium salt of N - (1 - benzylpiperid - 4 - yl) - 2 - hydroxy - 4 - amino - 5 - chlorobenzamide (5.1 g), m.p. 268—270°C (dec), was obtained.

EXAMPLE 3

To a stirred solution of 2 - benzyloxy - 4 - amino - 5 - chlorobenzoic acid (7.0 g; 0.025 moles) in anhydrous tetrahydrofuran (150 ml), triethylamine (2.5 g, i.e.

3.6 ml; 0.025 moles) was added. The resultant suspension was cooled to between −5° and −10°C and ethyl chloroformate (2.6 g, i.e. 2.4 ml; 0.025 moles) was added whilst maintaining this temperature. After stirring for half an hour, a solution of 1 - benzyl - 4 - aminopiperidine (4.8 g, 0.025 moles) in anhydrous tetrahydrofuran (20 ml) was added dropwise whilst maintaining the temperature at about −10°C. After one hour at this temperature, the reaction mixture was allowed to reach room temperature overnight. The solvent was removed under reduced pressure and the residue was treated with water, the aqueous mixture made alkaline and then extracted with chloroform. The organic solution was washed with water, dried (Na_2SO_4), decolourized and evaporated to dryness to give N - (1 - benzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - amino - 5 - chlorobenzamide (7.0 g). The solid was treated with ethanol saturated with hydrogen chloride to yield the hydrochloride monohydrate, m.p. 173—175°C.

Also prepared in a similar manner, using appropriate starting materials of general formulae IV and V, were

N - (1 - benzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 230—232°C (dec);

bis - [N - (1 - benzylpiperid - 4 - yl) - 2 - benzyloxy - 5 - methylsulphonylbenzamide]fumarate, m.p. 163°C;

N - [1 - (3,4,5 - trimethoxybenzyl)piperid - 4 - yl] - 2 - benzyloxy - 5 - methylsulphonylbenzamide, the fumarate of which melts at 183—185°C;

N - (1 - cinnamylpiperid - 4 - yl) - 2 - benzyloxy - 5 - methylsulphonylbenzamide, the fumarate of which melts at 195—197°C;

N - (1 - benzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamidobenzamide, the hydrochloride of which melts at 235—237°C;

N - (1 - *p* - chlorobenzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamidobenzamide, the hydrochloride hemihydrate of which melts at 191—193°C;

N - [1 - (3,4,5 - trimethoxybenzyl)piperid - 4 - yl] - 2 - benzyloxy - 4 - acetamidobenzamide, the hydrochloride of which melts at 247—249°C (dec);

N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - benzyloxy - 4 - acetamidobenzamide, the hydrochloride of which melts at 232—234°C (dec);

N - (1 - phenethylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamidobenzamide, the hydrochloride of which melts at 230—232°C (dec);

N - (1 - benzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide, the fumarate of which melts at 223—225°C;

bis - [N - (1 - *p* - methylbenzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide]fumarate, m.p. 205—207°C;

bis - [N - (1 - *p* - chlorobenzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide]fumarate, m.p. 208—210°C;

N - [1 - (2 - methoxy - 5 - chlorobenzyl)piperid - 4 - yl] - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide, the hydrochloride of which melts at 228—229°C;

bis - [N - [1 - (3,4,5 - trimethoxybenzyl)piperid - 4 - yl] - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide]fumarate, m.p. 203—205°C (dec);

N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide, the fumarate of which melts at 170—172°C;

N - (1 - phenethylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide, the hydrochloride of which melts at 194—196°C (dec);

N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - benzyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 204—206°C;

N - (1 - phenethylpiperid - 4 - yl) - 2 - benzyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 237—239°C (dec);

N - (1 - benzylpiperid - 4 - yl) - 2 - acetoxy - 4 - acetamido - 5 - chlorobenzamide, the hydrochloride of which melts at 226—228°C;

N - (1 - *p* - chlorobenzylpiperid - 4 - yl) - 2 - acetoxy - 4 - acetamido - 5 - chlorobenzamide, the hydrochloride of which melts at 243—245°C;

N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - acetoxy - 4 - acetamido - 5 - chlorobenzamide, the hydrochloride of which melts at 224—226°C (dec);

N - (1 - cinnamylpiperid - 4 - yl) - 2 - acetoxy - 4 - acetamido - 5 - chlorobenzamide, the fumarate of which melts at 174—176°C (dec);

N - (1 - benzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - trifluoroacetylamino - 5 - chlorobenzamide, the hydrochloride of which melts at 163—165°C;

N - [1 - (2 - thienylmethyl)piperid - 4 - yl] - 2 - benzyloxy - 4 - acetamidobenzamide, the hydrochloride of which melts at 244—246°C;

N - (1 - benzyl - 3 - methylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamidobenzamide, the fumarate of which melts at 219—221°C (dec);

N - (1 - cyclohexa - 1',4' - dienylmethylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamidobenzamide, the fumarate of which melts at 203—205°C (dec);

N - [1 - (2 - thienylmethyl)piperid - 4 - yl] - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide, the hydrochloride of which melts at 218—220°C;

N - (1 - benzyl - 3 - methylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide, the hydrochloride of which melts at 213—215°C;

N - (1 - cyclohexa - 1',4' - dienylmethylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide, the hydrochloride of which melts at 226—228°C;

N - (1 - *m* - trifluoromethylbenzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide, the fumarate of which melts at 226—228°C;

N - (1 - cyclohexa - 1',4' - dienylmethylpiperid - 4 - yl) - 2 - benzyloxy - 4 - amino - 5 - chlorobenzamide, the fumarate of which melts at 168—170°C;

N - (1 - cyclohexylmethylpiperid - 4 - yl) - 2 - benzyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 162—164°C;

N - [1 - (1 - cyclohexa - 1',4' - dienylethylpiperid - 4 - yl) - 2 - benzyloxy - 4 - amino - 5 - chlorobenzamide, the fumarate of which melts at 198—200°C;

N - (1 - cyclohexa - 1',4' - dienylmethylpiperid - 4 - yl) - 2 - acetoxy - 4 - acetamido - 5 - chlorobenzamide, the fumarate of which melts at 151—153°C;

N - (1 - cyclohexylmethylpiperid - 4 - yl) - 2 - acetoxy - 4 - acetamido - 5 - chlorobenzamide, m.p. 197—199°C;

N - (1 - cyclohexa - 1',4' - dienylmethylpiperid - 4 - yl) - 2 - benzyloxy - 5 - methylsulphonylbenzamide, the fumarate of which melts at 203—205°C;

N - methyl - N - (1 - benzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, the fumarate of which melts at 192—194°C (dec);

bis - [N - (1 - cyclohexa - 1',4' - dienylmethylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide]fumarate, m.p. 202—204°C (dec);

N - (1 - cyclohexylmethylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 218—222°C (dec);

N - (1 - benzylpiperid - 4 - yl) - 2 - propargyloxy - 5 - methylsulphonylbenzamide, the hydrochloride of which melts at 175—177°C (dec);

N - (1 - *p* - chlorobenzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 210—212°C (dec);

N - (1 - cinnamylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride monohydrate of which melts at 163—165°C;

N - [1 - (2 - thienylmethyl)piperid - 4 - yl] - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride hemihydrate of which melts at 223—225°C (dec);

N - (1 - phenethylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride monohydrate of which melts at 210—212°C (dec);

N - (1 - phenethylpiperid - 4 - yl) - 2 - propargyloxy - 4 - acetamido - 5 - chlorobenzamide, the fumarate of which melts at 199—201°C;

bis - [N - (1 - benzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - acetamido - 5 - chlorobenzamide]fumarate, m.p. 182—184°C;

N - (1 - *p* - methylbenzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 218—220°C (dec);

bis - [N - (1 - cyclohex - 3 - enylmethylpiperid - 4 - yl -) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide]fumarate, m.p. 191—193°C (dec);

N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride hemihydrate of which melts at 215—217°C (dec);

N - [1 - (3 - *p* - fluorobenzoylpropyl)piperid - 4 - yl] - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, the fumarate of which melts at 177—179°C;

N - (1 - diphenylmethylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, m.p. 190—192°C;

N - [1 - (3,4 - methylenedioxybenzyl)piperid - 4 - yl] - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 241—243°C (dec);

N - [1 - (1 - cyclohexa - 1',4' - dienylethyl)piperid - 4 - yl] - 2 -

propargyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 242—244°C (dec);

N - (1 - benzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - methylamino - 5 - chlorobenzamide, the hydrochloride of which melts at 233—235°C (dec);

N - (1 - cyclohexa - 1',4' - dienylmethylpiperid - 4 - yl) - 2 - propargyloxy - 4 - methylamino - 5 - chlorobenzamide, m.p. 146—148°C;

N - (1 - phenethylpiperid - 4 - yl) - 2 - propargyloxy - 4 - methylamino - 5 - chlorobenzamide, the fumarate of which melts at 184—186°C (dec);

N - (1 - benzylpiperid - 4 - yl) - 2 - chloro - 4 - aminobenzamide, the fumarate of which melts at 231—233°C (dec);

N - (1 - benzylpiperid - 4 - yl) - 2 - chloro - 4 - acetamidobenzamide, the fumarate of which melts at 198—200°C (dec);

N - (1 - phenethylpiperid - 4 - yl) - 2 - chloro - 4 - acetamidobenzamide, m.p. 146—148°C;

N - (1 - benzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - bromobenzamide, the hydrochloride monohydrate of which melts at 206—208°C (dec);

N - (1 - cyclohexa - 1',4' - dienylmethylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - bromobenzamide, m.p. 159—161°C;

N - (1 - phenethylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - bromobenzamide, the hydrochloride monohydrate of which melts at 205—207°C (dec);

N - [1 - (4 - methylcyclohexa - 1,4 - dienyl)methylpiperid - 4 - yl] - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 198—200°C (dec);

N - (1 - *p* - methoxybenzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 230—232°C (dec);

N - (1 - *p* - fluorobenzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride of which melts at 213—215°C (dec);

N - [1 - (2 - cyclohexa - 1',4' - dienylethyl)piperid - 4 - yl] - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide, the hydrochloride hemihydrate of which melts at 210—212°C (dec);

N - [1 - (4 - methylcyclohexa - 1,4 - dienyl)methylpiperid - 4 - yl] - 2 - propargyloxy - 4 - methylamino - 5 - chlorobenzamide, m.p. 209—211°C;

N - [1 - (4 - methylcyclohexa - 1,4 - dienyl)methylpiperid - 4 - yl] - 2 - propargyloxy - 4 - amino - 5 - bromobenzamide, m.p. 158—160°C;

N - ethyl - N - (1 - benzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide, m.p. 201—203°C (dec);

N - (1 - benzylpiperid - 4 - yl) - 2,5 - dichloro - 4 - aminobenzamide, the fumarate of which melts at 234—236°C (dec);

The fumarates mentioned above were obtained by adding fumaric acid in stoichiometric amount to a hot ethanolic solution of the piperidine base. The resulting hot solution was cooled and the fumarate crystallizes.

EXAMPLE 4

A suspension of N - (1 - phenethylpiperid - 4 - yl) - 2 - benzyloxy - 4 - amino - 5 - chlorobenzamide hydrochloride (5.0 g; 0.01 moles) [prepared by the procedure of Example 3] and 10% palladium/charcoal catalyst (0.5 g) in absolute ethanol (200 ml) was shaken under hydrogen (0.5 atm. pressure) for one hour at room temperature. The mixture was filtered, the residue washed with hot methanol and the organic solution concentrated *in vacuo*. N - (1 - phenethylpiperid - 4 - yl) - 2 - hydroxy - 4 - amino - 5 - chlorobenzamide hydrochloride (3.3 g) crystallizes, m.p. 273—275°C.

Also prepared in a similar manner from the corresponding 2-benzyloxy-benzamides were

N - (1 - benzylpiperid - 4 - yl) - 2 - hydroxy - 4 - acetamido - 5 - chlorobenzamide, the fumarate of which melts at 241—243°C;

N - (1 - *p* - methylbenzylpiperid - 4 - yl) - 2 - hydroxy - 4 - acetamido - 5 - chlorobenzamide hydrochloride, m.p. 247—249°C;

N - (1 - *p* - chlorobenzylpiperid - 4 - yl) - 2 - hydroxy - 4 - acetamido - 5 - chlorobenzamide hydrochloride, m.p. 269—270°C;

N - [1 - (2 - methoxy - 5 - chlorobenzyl)piperid - 4 - yl] - 2 - hydroxy - 4 - acetamido - 5 - chlorobenzamide hydrochloride, m.p. 199—201°C (dec);

N - [1 - (3,4,5 - trimethoxybenzyl)piperid - 4 - yl] - 2 - hydroxy - 4 - acetamido - 5 - chlorobenzamide hydrochloride, m.p. 268—270°C (dec);

N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - hydroxy - 4 - acetamido - 5 - chlorobenzamide hydrochloride, m.p. 271—273°C (dec);

N - (1 - phenethylpiperid - 4 - yl) - 2 - hydroxy - 4 - acetamido - 5 - chlorobenzamide hydrochloride, m.p. 313—315°C (dec);

N - [1 - (3,4,5 - trimethoxybenzyl)piperid - 4 - yl] - 2 - hydroxy - 4 - amino - 5 - chlorobenzamide hydrochloride, m.p. 265—267°C (dec);

N - (1 - benzylpiperid - 4 - yl) - 2 - hydroxy - 4 - trifluoroacetylamino - 5 - chlorobenzamide hydrochloride, m.p. 253—255°C;

N - (1 - benzylpiperid - 4 - yl) - 2 - hydroxy - 5 - methylsulphonylbenzamide hydrochloride, m.p. 296—298°C (dec), and

N - (1 - benzyl - 3 - methylpiperid - 4 - yl) - 2 - hydroxy - 4 - acetamido - 5 - chlorobenzamide, the fumarate of which melts at 249—251°C (dec).

The fumarates mentioned above were prepared by treating the free base (obtained from the hydrochloride by treatment with sodium bicarbonate) suspended in hot ethanol, with fumaric acid in stoichiometric amount. The resulting hot solution was cooled and the fumarate crystallizes.

EXAMPLE 5

A suspension of N - (1 - cyclohexylmethylpiperid - 4 - yl) - 2 - methoxy - 4 - acetamido - 5 - chlorobenzamide (5 g; 0.011 moles) [prepared by the procedure of Example 3], triethylamine (1.54 ml; 0.011 moles) and anhydrous aluminium chloride (2.6 g; 0.0195 moles) in 1,2-dichloroethane (150 ml) was boiled under reflux for 12 hours. The precipitate was filtered off, the solution poured into a saturated aqueous solution of sodium bicarbonate and the precipitate extracted with ethyl acetate. The organic solution was dried (Na_2SO_4), decolourized and the solvent removed *in vacuo*. The residue was triturated with diethyl ether to give 3 g of crude N - (1 - cyclohexylmethylpiperid - 4 - yl) - 2 - hydroxy - 4 - acetamido - 5 - chlorobenzamide. The compound was treated with a saturated solution of hydrogen chloride in methanol to give the hydrochloride salt, which was then recrystallized from methanol. Pure N - (1 - cyclohexylmethylpiperid - 4 - yl) - 2 - hydroxy - 4 - acetamido - 5 - chlorobenzamide hydrochloride (1.8 g), m.p. 272—274°C, was obtained.

EXAMPLE 6

A mixture of N - (1 - cinnamylpiperid - 4 - yl) - 2 - acetoxy - 4 - acetamido - 5 - chlorobenzamide (3.4 g; 0.0072 moles) [prepared by the procedure of Example 3], 8N sodium hydroxide aqueous solution (50 ml) and methanol (50 ml) was stirred for 72 hours at room temperature. Then the mixture was diluted with water, washed with chloroform and the aqueous solution acidified with concentrated hydrochloric acid and then made alkaline with sodium bicarbonate and extracted with chloroform. The organic solution was dried (Na_2SO_4), the solvent removed *in vacuo* and the residue triturated with diethyl ether to give a solid (1.8 g). This solid was suspended in hot ethanol and treated with the stoichiometric amount of fumaric acid to give a solution. On cooling this solution, N - (1 - cinnamylpiperid - 4 - yl) - 2 - hydroxy - 4 - acetamido - 5 - chlorobenzamide fumarate crystallizes, m.p. 212°—214°C (dec).

Also prepared in a similar manner was N - (1 - cyclohexa - 1',4' - dienylmethylpiperid - 4 - yl) - 2 - hydroxy - 4 - acetamido - 5 - chlorobenzamide fumarate, m.p. 219—221°C (dec).

EXAMPLE 7

A mixture of N - (1 - p - chlorobenzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide (5.26 g; 0.01 mole) [prepared by the procedure of Example 3], concentrated hydrochloric acid (5 ml), methanol (35 ml) and water (40 ml) was boiled under reflux for 1.5 hours. A viscous liquid is formed during the reaction which solidifies on cooling. Then the mixture was diluted with water, the methanal removed *in vacuo* and the solid collected by filtration. After recrystallization from ethanol, 3.8 g of N - (1 - *p* - chlorobenzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - amino - 5 - chlorobenzamide hydrochloride, m.p. 198°—200°C, were obtained.

Also prepared in a similar manner from the corresponding 4-acetamido-benzamides were

N - (1 - *p* - methylbenzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - amino - 5 - chlorobenzamide hydrochloride, m.p. 205—207°C;

N - [1 - (2 - methoxy - 5 - chlorobenzyl)piperid - 4 - yl] - 2 - benzyloxy - 4 - amino - 5 - chlorobenzamide hydrochloride, m.p. 241—243°C;

N - [1 - (3,4,5 - trimethoxybenzyl)piperid - 4 - yl] - 2 - benzyloxy - 4 - amino - 5 - chlorobenzamide hydrochloride, m.p. 229—231°C;

N - [1 - (1 - phenylethyl)piperid - 4 - yl] - 2 - hydroxy - 4 - amino - 5 - chlorobenzamide hydrochloride, m.p. 290—292°C (dec);

N - (1 - *p* - chlorobenzylpiperid - 4 - yl) - 2 - hydroxy - 4 - amino - 5 - chlorobenzamide, the fumarate of which melts at 221°—223°C;

N - [1 - (2 - thienylmethyl)piperid - 4 - yl] - 2 - benzyloxy - 4 - amino - 5 - chlorobenzamide hydrochloride monohydrate, m.p. 177°—179°C;

N - (1 - *m* - trifluoromethylbenzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - amino - 5 - chlorobenzamide hydrochloride, m.p. 239—240°C, and

N - (1 - cyclohexylmethylpiperid - 4 - yl) - 2 - hydroxy - 4 - amino - 5 - chlorobenzamide hydrochloride, m.p. 253—255°C.

The fumarate mentioned above was prepared from the corresponding hydrochloride by the procedures described at the end of Example 4.

EXAMPLE 8

A solution of N - (1 - benzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - trifluoroacetylamino - 5 - chlorobenzamide (8.2 g; 0.015 moles) [prepared by the procedure of Example 3] in methanol (50 ml), 8N sodium hydroxide aqueous solution (50 ml) and water (50 ml) was stirred for 48 hours at room temperature. Then the mixture was diluted with water, extracted with chloroform, the organic solution dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was treated with a saturated solution of ethanolic hydrogen chloride to give N - (1 - benzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - amino - 5 - chlorobenzamide hydrochloride monohydrate (6.4 g), m.p. 173—175°C.

EXAMPLE 9

A solution of N - (1 - cyclohexa - 1',4' - dienylpiperid - 4 - yl) - 2 - acetyloxy - 4 - acetamido - 5 - chlorobenzamide (4.2 g; 0.0094 moles) [prepared by the procedure of Example 3] in ethanol (20 ml), concentrated hydrochloric acid (4.2 ml) and water (50 ml), was boiled under reflux for 2 hours. Then the mixture was diluted with water, made alkaline with sodium bicarbonate and extracted with chloroform. The organic solution was dried (Na_2SO_4), the solvent removed *in vacuo* and the residue triturated with diethyl ether to give a solid (2.9 g). This solid was suspended in hot ethanol and treated with the stoichiometric amount of fumaric acid to given a solution. On cooling this solution, N - (1 - cyclohexa - 1',4' - dienylpiperid - 4 - yl) - 2 - hydroxy - 4 - amino - 5 - chorobenzamide fumarate crystallizes, m.p. 224—226°C (dec).

EXAMPLE 10

N,N' - dicyclohexylcarbodiimide (8.25 g; 0.04 moles) and 1 - benzyl - 4 - aminopiperidine (7.6 g; 0.04 moles) were added successively to a solution of 2 - acetoxy - 4 - acetamido - 5 - chlorobenzoic acid (10.8 g; 0.04 moles) in methylene chloride (250 ml). After stirring overnight at room temperature, the insoluble N,N' - dicyclohexylurea was filtered off, the solution was washed with water, dried (Na_2SO_4) and the solvent removed *in vacuo* to give a solid. It was treated with an ethanolic solution of hydrogen chloride to give N - (1 - benzylpiperid - 4 - yl) - 2 - acetoxy - 4 - acetamido - 5 - chlorobenzamide hydrochloride (12.0 g), m.p. 226—228°C.

EXAMPLE 11

A solution of 2 - benzyloxy - 4 - trifluoroacetylamino - 5 - chlorobenzoyl chloride (19.6 g; 0.05 moles) dissolved in anhydrous tetrahydrofuran (75 ml) was added little by little to another solution of 1 - benzyl - 4 - aminopiperidine (8.75 g; 0.046 moles) and triethylamine (6.45 ml; 0.046 moles) in anhydrous tetrahydrofuran (75 ml) at room temperature. On completion of the addition, the mixture was left at room temperature and stirred for 48 hours and then the mixture was concentrated *in vacuo*, poured into water and extracted with chloroform. The organic solution was dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was suspended in hot ethanol and treated with an ethanolic solution of hydrogen chloride to give N - (1 - benzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - trifluoroacetylamino - 5 - chlorobenzamide hydrochloride (17.5 g), m.p. 163—165°C.

EXAMPLE 12

To a solution of N - (1 - benzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide (3.16 g; 0.06 moles) [prepared by the procedure of Example 3] in acetone (150 ml) a solution of methyl iodide (1 ml; 0.016 moles) in acetone (20 ml) was slowly added. After stirring at room temperature for 10 hours, an additional amount of methyl iodide (1 ml; 0.016 moles) was added and the mixture left at room temperature overnight. The mixture was then evaporated *in vacuo* and N - (1 - benzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide methyl iodide (2.5 g) crystallizes, m.p. 229°—231°C.

Also prepared in a similar manner were

N - (1 - *p* - methylbenzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - amino - 5 - chlorobenzamide methyl iodide, m.p. 182°C, and

N - (1 - cyclohexa - 1',4' - dienylmethylpiperid - 4 - yl) - 2 - benzyloxy - 5 - methylsulphonylbenzamide methyl iodide, m.p. 192—194°C (dec).

EXAMPLE 13

A mixture of N - (1 - benzylpiperid - 4 - yl) - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide (9.84 g; 0.02 moles) [prepared by the procedure of Example 3], glacial acetic acid (50 ml) and 30% hydrogen peroxide solution (5.1 ml) was stirred for 12 hours at a temperature between 70° and 80°C. The solvent was removed *in vacuo*, the residue was treated with sodium hydroxide aqueous solution and then extracted with chloroform. The organic solution was dried (Na_2SO_4) and the solvent evaporated to dryness to give a solid which was washed with diethyl ether. N - (1 - Benzyl - piperid - 4 - yl) - 2 - benzyloxy - 4 - acetamido - 5 - chlorobenzamide N'-oxide (2.0 g) was obtained and then salified with fumaric acid by the procedure described at the end of Example 3 to give the fumarate salt, m.p. 153—155°C (dec).

The following Examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 14

100,000 tablets each containing 3 mg of N - (1 - benzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide hydrochloride were prepared from the following formulation:

N - (1 - benzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide hydrochloride	300 g
microcrystalline cellulose	1850 g
lactose spray dried	9620 g
carboxymethyl starch	570 g
sodium stearyl fumarate	80 g
colloidal silicon dioxide	80 g

Procedure:

All the powders were passed through a screen with an opening of 0.6 mm. They were then all mixed in a suitable mixer for 30 minutes and compressed into 125 mg tablets using 6 mm discs and flat bevelled punches. The disintegration time of the tablets was about 60 seconds.

EXAMPLE 15

100,000 capsules each containing 4 mg of N - (1 - benzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide hydrochloride were prepared from the following formulation:

N - (1 - benzylpiperid - 4 - yl) - 2 - propargyloxy - 4 - amino - 5 - chlorobenzamide hydrochloride	400 g
lactose	8500 g
sodium lauryl sulphate	370 g
corn starch	8200 g
alpine talc	530 g

Procedure:

The above ingredients were sieved through a 40 mesh sieve, then mixed in a suitable mixer and distributed into 100,000 gelatine capsules (180 mg).